REMARKS

The Office Action mailed September 16, 2008, and the Supplemental Office Action mailed November 26, 2008, have been received and carefully considered. Indication that claim 10 is allowed is acknowledged with thanks.

In this Amendment, the Title has been amended for linguistic reasons. A Second Substitute Specification is attached, as well as a Marked-up copy of the present Substitute Specification showing the changes made. Claims 1-15 have been cancelled because Applicant noted an inadvertent error in formulas (I) and (IV), and new claims 16-27 have been added. A new Abstract of the Disclosure is attached. To the best of the undersigned attorney's information and belief, these changes contain no new matter for the reasons given below.

Claims 16-27 are now pending in the Application and are submitted to be in allowable condition. Claims 16, 24, and 25 are independent.

Title Change and Support

The Title has been changes to "β –LACTAMASE-RESISTANT CEPHALOSPORIN ESTER COMPOUNDS AND SALTS THEREOF AND USE IN ORALLY-ADMINISTERED ANTIBIOTICS". This finds support on page 1 of the Application, Field of the Invention section, as well as in the examples where success in oral administration is shown.

Specification Changes and Support

As the attached marked-up copy of the Substitute Specification of record shows, the following changes have been made. The translation of "acetdimethylamide" has been corrected to "dimethyl acetamide" throughout. The Chinese character "或" has been changed to "or" (see the table under Example 1). A few inadvertent mistakes in the structures of the compounds has been corrected which Applicant submits would have been obvious mistakes to an artisan.

Claim Changes and Support

New independent compound claim 16 finds support in claim 9.

New claim 17 finds support in claim 14.

New claim 18 finds support in claim 7.

New claim 19 finds support in claim 8.

New method of use claim 20 finds support in claim 11.

New claim 21 finds support in claim 15.

New method of use claim 22 finds support in claim 15.

New claim 23 finds support in claim 15.

New claim 24 finds support in claim 10.

New claims 25 finds support in claims 6, 7, 8, 9 and 14.

New claim 26 finds support in claim 15.

New claim 27 finds support in claim 15.

I. The rejection of claims 1-8, 11-13, and 15 under 35 USC §112, second paragraph, is moot in view of cancellation of these claims so that this ground of rejection should be withdrawn. Moreover, the points raised by the Examiner in the Action have been carefully considered and Applicant believes are not present in new claims 16-27.

II. The rejection of claims 11 and 15 under 35 USC §101 is moot in view of cancellation of claims 11 and 15 so that this ground of rejection should be withdrawn. Moreover, new method of use claims 20 and 22 are phrased in process terminology and include steps as required.

III. The rejection of claims 1-9, 13, and 14 [sic claims 1-9 and 11-15] under 35 U.S.C. §103(a) as unpatentably obvious over Baltzer or English, these in view of Okonogi, 6150350, Crosby, Bauernfeind, Aubert, Xiong (1995), Fu, and Xiong (2004) is moot in view of cancellation of these claims and is submitted overcome by new claims 16-26 for the reasons given in the following.

The present invention relates to the mutual prodrug of β-lactam antibiotics and β-lactamase inhibitors, especially the mutual bis-esters prodrugs of cephalosporin and sulbactam.

Most of the references cited by the Examiner disclose the synergistic effect of sulbactam (β-lactamase inhibitors) with β-lactam antibiotics and this means that sulbactam and β-lactamase inhibitors must be used by mixed injections or infusions. Only the primary references Baltzer and English disclose the mutual prodrugs of β-lactam antibiotics and β-lactamase inhibitors, wherein the β-lactam antibiotics are penicillins.

Applicant notes that the references relied on by the Examiner were published more than 20 years ago. The Baltzer article was received for publication July 30, 1980. The English article was received for publication March 22, 1989. Applicant respectfully submits that in all that time, no β-lactamase resistant cephalosporin ester compounds have been reported, which is a fact that clearly supports Applicant's position that these compounds are difficult to obtain.

The present invention solves a technical problem which was desired to be solved for a long time but which had not be solved successfully. Applicant varied the specific performance and reaction conditions, and surprisingly successfully obtained a series of β-lactamase resistant cephalosporin ester compounds.

Baltzer or English taken with Okonogi, 6,150,350, Crosby, Bauernfeind, Aubert, Xiong (1995), Fu, and Xiong (2004) might be construed to give motivation for those of ordinary skill in this art to attempt to prepare the mutual prodrug of β-lactam antibiotics and β-lactamase inhibitors, but Applicant submits that the artisan would have difficulty in obtaining the mutual prodrug. This is because the confirmation of a compound requires not only the description of its structure, but also the preparation and identification of the compound.

The preparation of organic compounds is influenced by many factors, such as steric hinderance, reaction activity of groups, tension of rings and so on, which are due to differences of the parent nucleus and chain. For example, penicillin and cephalosporin both belong to β-lactam antibiotics, but the rings A in their parent nucleus structure are different, namely, the parent nuclear structure of penicillin is 6-APA, whereas that of cephalosporin is 7-ACA. The former is a hydrogenised thiazole ring, while the latter is a thiazine ring.

While preparing mutual double-ester prodrugs, Sulbactam reacts with penicillin or cephalosporin. Although the two technical solutions are similar, the specific performance and reaction conditions are different due to the differences between the structures of penicillin and

cephalosporin.

The inventor of the present invention varied the specific performance and reaction conditions, and surprisingly successfully obtained a series of β-lactamase resistant cephalosporin ester compounds.

Further, Applicant respectfully draws the Examiner's attention to the fact that the compounds of the present invention, i.e., see claims 16, 17, and 25, themselves produce an unexpected antibacterial effect.

The prior carboxyl-terminated double-ester prodrugs have no antibacterial effects *in vitro*. Only after oral delivery, absorption and hydrolysis do the parent drugs from these mutual prodrugs show antibacterial effect. In contrast, the compounds of the present invention have excellent antibacterial effect *in vitro*.

For example, Applicant's effectiveness Example 1 shows the antibacterial activity *in vitro* of compounds TR-1 and YR-2. According to this experiment, Applicant demonstrates that both YR-1 and YR-2 have antibacterial activity *in vitro* which is nearly equal to that of the combination of parent drugs, and, for some bacterial strains, such as Proteus mirabilis, Bacillus preteus, Proteus morganii and Shigella flexneri, the antibacterial activities of YR-1 and YR-2 are veen better than that of the combination of parent drugs. Applicant respectfully submits that the above effects would not be obvious to one of ordinary skill in the art.

In summary, the present invention is submitted to be novel, useful, and unobvious. The present invention has prominent substantive features and represents notable progress, and possesses inventiveness. Thus, it is Applicant's position that the combined disclosures of Baltzer or English taken with Okonogi, 6,150,350, Crosby, Bauernfeind, Aubert, Xiong (1995), Fu, and Xiong (2004) do not meet Applicant's new claims 16-27 so that these combinations do not set out a *prima facie* case of obviousness against new claims 16-27.

IV. The Office Action mailed September 16, 2008, objected to claim 9 and 14 as being dependent upon a rejected base claim, but allowable if rewritten in independent form. This was in error in view of which the Examiner issued a Supplemental Office Action dated November 26, 2008 and restarted the date for responding.

The Supplemental Office Action showed that claim 10 is allowed and claims 1-19 rejected. This was clarified by the Examiner as claim 10 is allowed and claims 1-9 and 11-15 are rejected

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that new claims 16-27 and the Application are in condition for allowance. Reconsideration and passage of this case to issue are therefore requested.

Should the Examiner consider that a conference would help to expedite the prosecution of this Application, the Examiner is invited to contact the undersigned to arrange for such an interview.

No fee is believed due since there are now three independent claims and 12 total claims. If any fee is deemed due, the Commissioner is hereby authorized to charge the same to our Deposit Account No, 18-0002 and is requested to advise us accordingly.

Respectfully submitted,

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Date

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